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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/493,427	01/29/2000	Patrick L. Iverson	0450-0025.30	2225

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PERKINS COIE LLP
P.O. BOX 2168
MENLO PARK, CA 94026

EXAMINER
EPPS, JANET L

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/493,427	Applicant(s) IVERSON ET AL.	
	Examiner Janet L Epps-Ford, Ph.D.	Art Unit 1635	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 8-22-02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/493,427 is acceptable and a CPA has been established. An action on the CPA follows.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have added new claim 34, wherein claim 34 recites "[T]he method of claim 33, wherein the amount of antisense compound administered is between about 1 and 12.5 mg. According to Applicants support for this newly added claim could be found in original claim 5 and page 11, lines 8-13. Original claim 5, and page 11 of the specification provide support for wherein the amount of antisense compound administered is between about 0.5 and 20 mg. The specification as filed provides support for wherein the amount of antisense compound delivered to a vessel site is between about 0.5-2 mg, or preferably between 5 and 20 mg, in a total volue of between about 0.2 to 1 ml. However, neither original claim 5 nor Applicants specification

provide support for this newly added claim, wherein the amount of antisense compound administered is between about 1 and 12.5 mg.

Applicants must remove the new matter recited in claim 34 in response to this amendment.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 29 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29 and 42 (and those claims dependent therefrom) recite structures which correspond to intersubunit linkages, however these claims do not provide definitions of the variables recited in these structures according to Pi, Pj, X, Y, Y1, Y2, and Z. Therefore, the metes and bounds of these claims are vague and indefinite since the structures recited in the claims are unclear.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 28, 32, 34-36, and 41 are rejected under 35 U.S.C. 102(e) as being anticipated by Zalewski et al. (US Patent 6,133,242).

Claim 28, 32, and 35, recite a method for treating a vascular injury site by reducing restenosis at the site, said method comprising administering to a patient, by intravascular delivery directly to the vascular injury site, a morpholino antisense compound (i) having 8-40 nucleotides, including a targeting base sequence that is complementary to a region that spans the start codon of a human c-myc mRNA gene, and (ii) uncharged, phosphorus-containing intersubunit linkages, in an amount effective to reduce restenosis in the patient. Claim 32 recites the method of claim 28, wherein administering is carried out by injecting the antisense compound from an injection balloon catheter directly into the vascular injury site, under pressure, through injectors contained on the surface of the catheter balloon, wherein the vascular injury site comprises a vascular wall having a tunica media and wherein said injectors are capable of penetrating the tunica media in the vascular wall. Claim 34 recites the method of claim 28 wherein the amount of antisense compound administered is between about 1 and 12.5 mg. Claim 35 recites the method of claim 28, wherein said administering is carried out by contacting the vascular injury site with an intravascular stent having a coating containing the antisense compound in diffusable form. Claim 36 recites the method of claim 28, wherein the majority of the antisense compound is released over a period of 5-60 minutes following balloon angioplasty. Claim 41 recites an intravascular stent for treating vascular injury.

Zalewski et al. teach antisense oligonucleotides targeting human *c-myc* for the treatment of excess extracellular matrix in the tissues of a patient. The antisense oligonucleotides of Zalewski et al. may comprise morpholino modifications and modified phosphorous containing intersubunit linkages such as phosphorothioate, phosphorodithioate, phosphoramidate, or methylphosphonate. The antisense oligonucleotides of the Zalewski et al. invention have lengths

in the range of about 12 to about 60 nucleotides, preferably in the range of about 15 to about 40 and most preferably they have lengths in the range of about 18 to 30 nucleotides (col. 9, lines 15-21). The antisense oligonucleotides of this invention are preferably targeted to the initiation codon site, the mRNA donor splice site, the 5' cap site, tRNA primer binding site, and the mRNA acceptor splice site (col. 7, lines 5-10).

Zalewski et al. also teach that the disclosed antisense oligonucleotides can be used for intravascular application, in order to prevent restenosis after angioplasty. The antisense oligonucleotides are preferably administered in the vicinity of the lesion via catheter (i.e. stent) from inside the lumen, or through the adventitia (i.e. the most outer layer of the vessel wall) with materials aiding a slow release of antisense compound, e.g. a pluronic gel system, a porous balloon or iontophoretic balloon (col. 10, lines 55-67). Additionally, the Zalewski et al. invention comprises the use of sustained release systems suitable for administration of the antisense oligonucleotide compositions, these systems include semi-permeable polymer matrices in the form of films, microcapsules, or the like, comprising polylactides, copolymers of L-glutamic acid and gamma-ethyl-L-glutamate, poly(2)-hydroxyethyl methacrylate), and like materials. These sustained release systems also include liposomally entrapped antisense compounds (col. 16-27). In a preferred embodiment of Zalewski et al., the dose range of antisense compound delivered to the site of injury is between 1 μg to 1 mg and the delivery time is in the range of about 30 seconds to 60 minutes (col. 11, lines 1-8).

Zalewski et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

7. Claims 28, 32, 34-36, and 41 are rejected under 35 U.S.C. 102(e) as being anticipated by Zalewski et al. (US Patent 6,159,946)

Zalewski et al. also teach that the disclosed antisense oligonucleotides can be used for intravascular application, in order to prevent restenosis (col. 9, lines 41-45). In particular, an antisense compound of 15 nucleotides in length which comprises the following sequence: 5'-AACGTTGAGGGGCAT-3' (col. 8, lines 40-42), this sequence comprises 14 contiguous nucleobases of SEQ ID NO: 1 of the instant application. The antisense oligonucleotides of Zalewski et al. may comprise morpholino modifications and modified phosphorous containing intersubunit linkages such as phosphorothioate, phosphorodithioate, phosphoramidate, or methylphosphonate (col. 7, lines 1-23).

The antisense oligonucleotides of Zalewski et al. are preferably administered in the vicinity of the lesion via catheter (i.e. stent) from inside the lumen, or through the adventitia (i.e. the most outer layer of the vessel wall) with materials aiding a slow release of antisense compound, e.g. a pluronic gel system, a porous balloon or iontophoretic balloon (col. 10, lines 16-26). In a preferred embodiment of Zalewski et al., the dose range of antisense compound delivered to the site of injury is between 1 μg to 5 mg and the delivery time is in the range of about 30 seconds to 60 minutes (col. 10, lines 29-32).

Zalewski et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 28-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zalewski et al. (US Patent 6,13,242) or Zalewski et al. (US Patent 6,159,946) as discussed above in view of Kobayashi et al., Summerton et al., Agrawal et al., and Wolff et al. (US Patent No. 5,871,535 or 5,997,468).

The discussion of both Zalewski et al. references as set forth above is included in this rejection. [It is noted that the claims are examined to the extent that terms Pi and Pj recited in claims 29-31, 38-40, and 42-48, are as defined on page 9, lines 5-6, of the specification as filed]. Zalewski et al. discloses a method for preventing restenosis in a patient comprising the administration of antisense oligonucleotides comprising a morpholino and modified phosphorous containing intersubunit linkages, to the site of injury in a patient. However, Zalewski et al. does not teach the administration of a c-myc antisense oligonucleotides comprising the nucleotides sequence as set forth in SEQ ID NO:1 of the instant application, nor does Zalewski et al. teach the phosphorodiamidate linkage represented at Figure 2B-B, where X=NH_2, Y=O, and Z=O. Zalewski et al. does not teach the administration of antisense oligonucleotides in a solution containing at least about 30 mg/ml of the antisense compound. Zalewski et al. does not teach the use of a derivatized antisense compound comprising a triethyleneglycol moiety, or a stent

comprising said antisense compound. In addition, Zalewski et al. does not teach wherein the intravascular stent (or catheter) is biodegradable.

Kobayashi et al. teach the use of antisense oligonucleotides targeting the translation initiation sites of c-myc. These antisense oligonucleotides suppressed the proliferation of MKN-45, a human gastric cancer-derived cell line, and DLD-1, a human colon cancer-derived cell line, in vitro and in vivo. The antisense oligonucleotides comprise phosphorothioate type modifications. The c-myc AO suppressed MKN-45 cell proliferation in vitro at concentration from 0.1-10 mM, and 70% of suppression was obtained with 3-10 mM concentration. The AO decreased the ratio of c-myc positive cells, and the intracellular concentration of c-myc mRNA. Intratumor injection of AO for c-myc (27 mer, AACGTTGAGGGGCATCGTCGCGGGAGG, 10 mM) suppressed the tumor growth of MKN-45 transplanted to the BALB/c mouse. The c-myc antisense oligonucleotide of Kobayashi et al. comprises the nucleotide sequence of SEQ ID NO: 1 of the instant application (abstract).

Summerton et al. disclose alpha-morpholino ribonucleoside derivatives and polymers thereof, which are capable of sequence-specific binding to polynucleotides. These alpha-morpholino subunits form stable uncharged linkages and can be used to generate polymers having an uncharged backbone. According to Summerton et al., standard ribo- and deoxyribonucleotide polymers suffer from a number of limitations when used for base-specific binding to target oligonucleotides. These limitations include (i) restricted passage across biological membranes, (ii) nuclease sensitivity, (iii) target binding which is sensitive to ionic concentration, and (iv) susceptibility to cellular strand separating mechanisms. Furthermore, Summerton et al. state that these limitations can be overcome or minimized by designing

polynucleic acid analogs in which the bases are linked along an uncharged backbone (col. 2, lines 10-23).

Agrawal et al. teach modifications which enhance oligonucleotide solubility. In one embodiment Agrawal et al. discloses oligonucleotides comprising a triethyleneglycol moiety (col. 4, lines 8-12).

Wolff et al. (US Patent NO. 5,997,468, and 5,871,535) teach stent designs and materials, including biodegradable stents with release compound upon biodegradation, or which include a coating containing the compound in diffusible form, as admitted by Applicants on page 13, lines 12-15, of the specification as filed.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to modify the method of preventing restenosis in a patient as described by Zalewski et al. with the antisense oligonucleotide of Kobayashi et al. because this antisense oligonucleotide has been disclosed to function successfully in vitro and in vivo to reduce the expression of c-myc. Furthermore, one of skill in the art would have been motivated to use the antisense oligonucleotides of Kobayashi et al. because it would have been obvious to replace one functionally equivalent antisense oligonucleotide targeting c-myc with another. In addition, it would have been obvious to one of ordinary skill in the art to modify the antisense oligonucleotides of Zalewski et al. with the alpha-morpholino modified subunits of Summerton et al. since these polymers comprising these subunits are disclosed as being capable of overcoming the limitations described above that are associated with polymers comprising a charged backbone. One of ordinary skill in the art would have been motivated to use the modified polymers of Summerton et al. in the method of Zalewski et al., because using polymers

having enhanced biological activity would provide a means to increase the therapeutic efficacy of potential pharmaceutical agents.

Moreover, it would have been obvious to one of ordinary skill in the art to modify the oligonucleotides of Zalewski et al. with triethyleneglycol modifications as described by Agrawal, since these modifications enhance the solubility of the antisense oligonucleotides. Furthermore, one of ordinary skill in the art would have been motivated to use antisense oligonucleotides having enhanced solubility as modified by the method of Agrawal et al. since these antisense oligonucleotides are to be used in an aqueous biological environment. Agrawal et al. also teach that these moieties can be used to form oligonucleotide multimers, such multimers would enhance the effective concentration of the oligonucleotide and therefore increase the efficacy of an antisense compound.

Additionally, it would have been obvious to one of ordinary skill in the art at the time of filing to modify the teachings of Zalewski et al. to comprise the use of the biodegradable stents disclosed in the Wolff et al. references. One of ordinary skill in the art would have been motivated to make this modification since biodegradable stents of Wolff et al. are disclosed as being useful for the same purpose as the delivery devices disclosed by Applicants, particularly for administering antisense compounds to an injured vascular region, and furthermore, as required for the administration of the compounds of Zalewski et al. (col. 10, lines 55-67). It is *prima facie* obvious to substitute one functionally equivalent stent for another, to be used for the same disclosed purpose as recited in the instant claims.

Applicant's method recites the use of an antisense compound in an amount of about 0.5 to 2 mg or in a solution containing at least about 30 mg/ml. Zalewski et al. teach the use of

antisense oligonucleotides in their disclosed methods in amount of between about 1 to 100 μM and more preferably between 1 to 10 μM. Although the method of Zalewski et al. does not recite the exact amount of antisense compound as recited in Applicant's method, absent evidence to the contrary it would have been obvious to one of ordinary skill in the art to optimize the conditions of an experiment or reaction in order to maximize the desired results.

Therefore, the invention as a whole is *prima facie* obvious over Zalewski et al. (US Patent 6,13,242) or Zalewski et al. (US Patent 6,159,946) in view of Kobayashi et al., Summerton et al., Agrawal et al. and Wolff et al. (both references).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
October 30, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635